

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



Europäisches Patentamt
European Patent Office
Office européen des brevets

11 Publication number:

0 381 446
A1

12

EUROPEAN PATENT APPLICATION

21 Application number: 90300953.8

51 Int. Cl.5: A61K 6/00, A61K 9/70,
A61K 31/415, A61K 31/71,
A61K 47/32, A61K 47/34,
A61K 47/38

22 Date of filing: 30.01.90

23 Priority: 31.01.89 US 304092
18.01.90 US 465786

24 Date of publication of application:
08.08.90 Bulletin 90/32

25 Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

26 Applicant: YISSUM RESEARCH DEVELOPMENT
COMPANY OF THE HEBREW UNIVERSITY OF
JERUSALEM
46, Jabotinsky Street P.O. Box 4279
Jerusalem 91042(IL)

27 Inventor: Friedman, Michael
11 Ein Gedy Street
Jerusalem 93833(IL)

28 Representative: Sheard, Andrew Gregory et al
Kilburn & Strode 30, John Street
London WC1N 2DD(GB)

54 Oral antifungal compositions.

55 Oral compositions for prevention of microfungal and mycotic infections of the oral cavity are disclosed comprising an antifungal compound embedded in a sustained release carrier such as a cellulosic polymer. Such oral compositions may contain an adhesive and a plasticizer to increase antifungal effectiveness, and may be coated onto orthodontal appliances such as dentures.

EP 0 381 446 A1

ORAL ANTIFUNGAL COMPOSITIONS

The invention is directed to an antimycotic composition for the prevention of microfungal infections of the oral cavity and to the use of such a composition in medicine and the preparation of an agent for treating mycotic diseases of the oral cavity caused by microfungi.

Microfungi can be classified as yeasts and filamentous fungi. Microfungi are capable of causing a variety of diseases in the oral cavity and the surrounding area. Mycotic diseases may arise as part of a systemic microfungal infection or may be derived from an independent infection which establishes in the oral cavity. Oral mycoses and their treatment are an important problem in oral medicine and have been reviewed in Kostiala, I. et al., Acta Odontol. Scand. 37:87-101 (1987).

Many factors can predispose a patient to an opportunistic microfungal infection in the oral cavity. For example, general debilitation or poor oral hygiene are predisposing factors. Patients who are being treated with antibiotics, steroids, or cytostatic therapy, patients with AIDS, diabetes mellitus or other immunodeficiency or hormonal diseases, patients with malignant tumors or a hematogenous disorder are all at a high risk for opportunistic fungal infections. In addition, certain age groups such as infants, the elderly, and pregnant women are at a higher risk of oral fungal infections.

Mechanical trauma from an ill-fitted prosthesis is also a major cause of oral microfungal infections. One report estimated that Candida was involved in 60% of the cases of "denture sore mouth" (denture stomatitis) in the elderly (Budtz-Jørgensen, E. et al., Community Dent. Oral Epidemiol. 3:115 (1975)). Denture stomatitis appears to be a manifestation of a cell-mediated hypersensitivity reaction to the microfungal infection.

It is important to treat oral mycotic infections as soon as possible. Untreated infections may become the foci for systemic dissemination of the yeast or fungus, with potentially fatal results in severely compromised patients. For example, disseminated candidosis is the second most common opportunistic infection in patients with AIDS (Odds, F.C., CRC Crit. Rev. Microbiol. 15:1-5 (1987)).

The most important species of microfungi which have been implicated as being involved in superficial or deep mycotic infections in the oral cavity include Candida albicans, C. tropicalis, C. stellatoidea, C. pseudotropicalis, C. parapsilosis, C. guilliermondii, C. krusei, and C. vixwanathii, all of which have been implicated in candidosis; Torulopsis glabrata which is the cause of torulpsidosis; Geotrichum candidum, which is the cause of geotrichosis; Rhizopus, Mucor, Absidia, and Basidiobolus which are the cause of aspergillosis, Cryptococcus neoformans, the cause of cryptococcosis; Blastomyces dermatitidis, the cause of blastomycosis; Paracoccidioides brasiliensis, the cause of paracoccidioidomycosis; Sporothrix schenckii, the cause of sporotrichosis; Rhinosporidium seeberi, the cause of rhinosporidiosis; Histoplasma capsulatum, the cause of histoplasmosis; Histoplasma duboisi, the cause of African histoplasmosis, Coccidioides immitis, the cause of coccidioidomycosis, Trichophyton mentagrophytes, T. rubrum, T. tonsurans, and T. violaceum, the causes of dermatophytosis; and, Rhinocladiella or Phialophora, and Cladosporium, the causes of chromomycosis.

The Candida species is the most virulent of the fungi which infect the oral mucosa. Pathogenic Candida species are aerobic yeasts that can also grow anaerobically. C. albicans, the Candida species most often responsible for infections of the oral cavity, grows in two morphological forms: either as a budding yeast, or as a continuously extending hyphae which extends into tissue. In the oral cavity, Candida may cause a variety of disorders based on localization of the infection such as pulpitis, gingivitis, tonsillitis, cheilitis, glossitis, stomatitis, pharyngitis, laryngitis and sinusitis.

Oral candidosis has been classified into different categories based on the clinical and histopathological manifestations of the infection (Lehner, T., in Clinical Aspects of immunology, P.G.H. Gell, et al., eds., 3rd edition, Blackwell Scientific Publications, Oxford, 1975, pp.1387-1427).

Acute pseudomembranous candidosis, or thrush, primarily affects children or patients with debilitating diseases (Crawson, R.A., Dent. Res. 15:361-364 (1965)). C. albicans is a major causative agent of thrush in the newborn.

The clinical signs which usually appear first are creamy-white, soft, nonkeratotic plaques which appear on the mucosa of the tongue, cheeks, gum and pharynx. The plaque is easily rubbed off, leaving an inflamed mucosa underneath. There may be no subjective symptoms until the plaque spreads to the pharynx, larynx or esophagus, where it may cause dysphagia, soreness and dryness of the tongue, a sore throat or symptoms of cheilitis.

Acute atrophic candidosis is a form of thrush which is consistently painful, and which is thought to arise as a consequence of the shedding of the fungal plaque from its site of attachment to the tissue. It can be found on the dorsum linguae, or associated with angular cheilitis and inflammation of cheeks and lips.

Chronic atrophic candidosis, or denture stomatitis is the term given to Candida-based infections of the denture-bearing tissues. Torulopsis glabrata is also associated with some forms of denture stomatitis.

Chronic mucocutaneous candidosis refers to four different types of candidosis which are resistant to treatment and which are associated with patients with a heterogeneous pattern of immunodeficiencies.

5 These types of candidosis include chronic oral hyperplastic candidosis, which predominately affects adult males between the ages of 30 and 70; chronic localized mucocutaneous candidosis, which starts in childhood as an intractable oral Candida infection and later manifests itself as lesions in the nails, and skin of the fingers and toes; chronic localized mucocutaneous candidosis with granuloma which primarily affects young girls, starting in the mouth but later manifesting itself as horny masses of the face, scalp and upper respiratory tract; and, chronic localized mucocutaneous candidosis with endocrine disorder, also found most frequently in young girls, and associated with lesions of the tongue, cheek, oral commissures and nails.

10 The establishment of a mycotic infection in the oral cavity presents a serious health problem to the host which must be treated and contained. Treatment of mycotic diseases is directed to controlling this flora.

15 The most widely used approach to date to control microfungi in the oral cavity has been mechanical cleaning methods such as brushing the teeth. Although this method has proved to be fairly successful in treating individuals, there is still a high recurrence rate. There is also the problem of motivating people to good oral hygiene habits that they will maintain throughout their lives.

20 Systemic administration of antimycotics per os or intravenously has been used to control mycotic infections, however, discontinuation of therapy often results in the return of the pathogens to the oral cavity. Long-term systemic antimycotic therapy in doses high enough to control oral infections are undesirable for treatment of oral infections because the potential dangers and side-effects associated with this form of treatment include the development of resistant strains and superimposed infections, gastrointestinal irritation, liver damage and neurological symptoms, among others.

25 Antifungal agents have also been used in the form of mouth rinses, dentifrices, solutions and gels but have not proven to be completely successful in preventing fungal infections. A main problem with these techniques is that the antifungal drug does not remain in the oral cavity long enough at efficacious levels.

30 Another serious problem with antifungal drugs is that they are by necessity directed towards controlling an infection by a eukaryotic fungal cell in a eukaryotic host. As a result, drugs effective against the fungus also tend to be toxic to the host. Thus it is important to develop methods which permit the localized, sustained application of the toxic drug in a manner and dosage which is efficacious but which minimizes toxicity to the host. Especially, it is important to develop methods which use low doses of the drug.

35 A topical, sustained-release form of an antifungal agent, could help maintain a locally efficacious level of the antifungal drug in the oral cavity and prevent these side effects. Such a dosage form might also prevent undesirable systemic side effects by releasing the drug at a lower therapeutic level over a long period of time in a localized manner. Ridgway, F. et al., U.S. 4,725,440, describes a soft, antifungal drug-containing pastille or troche which is free of rough edges and will not adhere to oral mucosa, but which only releases anti-fungal medications within the 15-90 minutes while it dissolves in the mouth.

40 Cyr et al., US 3,312,594 describes long lasting troches or pastilles for the treatment of oral lesions which include an anhydrous adhesive based on pectin, gelatin and carboxymethylcellulose and which, when wetted, adhere to the oral mucous membranes. However, the Cyr formulation was not well-tolerated by patients (Ridgway, F. et al., U.S. 4,725,440).

45 Sustained release has been reported to be achieved by embedding chlorhexidine in an ethyl cellulose polymer to form a varnish (Friedman, M., et al., J. Perio. Res. 17:323-328 (1982); Friedman, M., et al., IADR Prog. and Abstr. 59:No. 905 (1980)). This dosage form was used in the local treatment of periodontal disease (Soskolne, W.A., et al., J. Perio. Res. 18:330-336 (1983)) and in the treatment of plaque prevention in patients wearing orthodontic appliances (Friedman, M., et al., J. Dent. Res. 64:1319-1321 (1985)). A drawback to this plaque preventative system was that although plaque accumulation was decreased by the application of a varnish composed of chlorhexidine embedded in an ethyl cellulose polymer, the effectiveness of the system in decreasing plaque accumulation was present only for a period of four days subsequent to administration of the varnish. Friedman et al., (J. Dent. Res., supra), concluded that "clearly the conditions in the oral cavity and the formulation used do not, at present, facilitate such prolonged prevention of plaque accumulation." These authors also suggested that by altering the varnish components and method of preparation it might be possible in clinical use to sustain the necessary level of antibacterial agent release for longer periods. No suggestion was made in this publication as to how this could be accomplished.

55 Mastic has been used previously for dental purposes. U.S. Patent No. 4,668,188 (Wolfenson, G.B.) discloses the use of a curable mastic in the production of an oral impression tray for making impressions of teeth and jaw structures. Mastics have been used in the production of dental molds (U.S. Patent No.

4,500,288, VonWeissenfluh, H.), as an adhesive to secure dental articulators (U.S. Patent Nos. 4,548,581 and 4,382,787, Hoffman, R.E.) and as a tooth decay preventative (U.S. Patent No. 4,374,824, Wahmi). U.S. Patent Nos. 4,532,126 and 4,428,927 (Ebert, W.R., et al.) disclose chewable, filled, one-piece soft elastic gelatin capsules, made chewable by a masticatory substance, such as a synthetic mastic.

5 U.S. Patent No. 4,459,277 (Kosti, C.M.) relates to novel plaque compositions for use in evaluating oral hygiene practices. In brief, the patent discloses a water-insoluble, water-immiscible dye emulsified in fine droplets or rupturable capsules. The patent discloses the use of mastic resin as well as alginates, and other gums as an insoluble media for dye dispersion. In particular, sodium carboxymethylcellulose is disclosed. Also disclosed is the possibility of incorporating antibacterial agents such as stannous fluoride into the compositions. Significantly, the Kosti patent is concerned with diagnostic rather than therapeutic applications. The patent fails to suggest compositions exhibiting long-term preventive activity.

10 The background art fails to identify any compositions of matter comprising an effective antifungal agent together with a long-term sustained-release carrier, in combination with an adhesive polymer such as a mastic and a plasticizer such as polyethylene glycol, for use as an antifungal preventative varnish in the oral cavity by humans and other animals, under conditions in which the antimycotic agents have no deleterious medical side effects, and do not cause staining of the teeth. Another highly desirable characteristic not found in the art of record is that the antifungal agent should be released from the composition, not only in a sustained fashion, but over a sufficiently long period of time so as not to require excessive application of the composition.

15 20 With this in mind, the present inventor set out to find an oral antimycotic preventative composition which contains an antifungal agent effective against those microfungi that are responsible for oral infections, said composition being such that the antifungal agent can be released at efficacious levels in a sustained, long-term fashion, and such that the antifungal composition has the property of long-term adhesion to the oral tissue and teeth, and such that the antifungal composition remains plastic during the entire period of application.

25 With this goal in mind, the applicants have discovered an antifungal preventative composition with these desirable characteristics.

According to a first aspect of the present invention there is provided a sustained release oral antifungal varnish composition comprising:

30 (a) (an efficacious amount of) an antimycotic drug;
 (b) a sustained release hydrophobic polymer, and a pharmaceutically acceptable carrier.
 Preferred antimycotic drugs are nystatin and amphotericin B, as well as miconazole and clotrimazole. The pharmaceutical acceptable carrier is preferably water, or an alcohol (eg. C₁-₆ alcohol) such as ethanol, or a mixture thereof.

35 The composition may additionally comprise one or more of the following:

- (a) a flavouring agent;
- (b) a surface active agent;
- (c) a colouring agent;
- (d) a plasticiser such as polyethyleneglycol, glycerol, or sorbitol;
- (e) a mineral oil;
- (f) an adhesive gum such as gum mastic.

40 A second aspect of the present invention relates to the composition of the first aspect for use in human or veterinary medicine.

A third aspect of the present invention relates to the use of a composition comprising:

45 (a) an antimycotic drug;
 (b) a sustained release hydrophobic polymer;
 (c) a pharmaceutically acceptable carrier; in the preparation of a sustained release oral antifungal agent for the treatment of a microfungal infection.

A fourth aspect of the present invention relates to a process for the preparation of a sustained release oral antifungal varnish composition, the process comprising admixing:

- (a) an antimycotic drug;
- (b) a sustained release hydrophobic polymer; and
- (c) a pharmaceutically acceptable carrier.

A fifth aspect of the present invention relates to an orthodontal appliance having a surface at least partially coated with a sustained release oral antifungal varnish composition comprising:

- (a) an antimycotic drug;
- (b) a sustained release hydrophobic polymer; and
- (c) a pharmaceutically acceptable carrier.

According to a sixth aspect of the present invention there is provided a method of making an orthodontal appliance, the method comprising applying to at least part of a surface of an orthodontal appliance a sustained release oral antifungal varnish composition comprising:

- 5 (a) an antimycotic drug;
- (b) a sustained release hydrophobic polymer; and
- (c) a pharmaceutically acceptable carrier.

In the following description preferred features and characteristics of one aspect of the present invention are applicable to another aspect mutatis mutandis.

The antifungal composition may be applied to the teeth, gingival tissues of a human or animal, e.g. 10 domestic animal or an orthodontic appliance by a brush, by spray or by dipping.

Thus the present invention encompasses a composition comprising an antifungal agent embedded in a sustained release carrier composed of a cellulose polymer, in a pharmaceutically acceptable vehicle, optionally containing a plasticizer such as polyethylene glycol and/or an adhesive polymer such as gum mastic.

15 The invention thus encompasses oral compositions that may provide sustained, efficient, inexpensive, localized antifungal activity in the oral cavity at efficacious levels without deleterious side effects, and methods for using such compositions.

By "oral cavity" is meant the mouth and the surrounding esophageal area. Therefore, for example, the oral cavity includes the tongue, gums, palate, throat, teeth, tonsils and periodontal tissue.

20 By "sustained-release" is meant the continuous release of an active substance at efficacious levels for a prolonged period of time, such as 2-4 weeks or longer. The release of the active substance may be constant or pulsed, as long as efficacious levels of the active substance are provided to the surrounding milieu for the desired period of time.

By an "efficacious level" is meant a level or concentration of a drug or other active agent which is high enough to be effective in treating the condition the drug was designed to treat.

25 By "oral varnish" is meant a composition which is topically applied to a hard surface such as a tooth or orthodontic appliance and which dries as a film adhering to that surface, in a manner which resists removal under normal conditions, such as eating or brushing the teeth.

30 The compilation of the components of the aforementioned oral composition is based upon the specific properties of each of the individual components, wherein each component of the combination increases the antifungal effectiveness of other members of the combination.

In this specification antifungal agent and antimycotic agent are used interchangeably.

35 The oral composition of the invention may assist in the prevention of microfungal infections of the oral cavity and periodontal tissue, and in the relief of symptoms resulting from existing microfugally-causing problems, by attacking the pathogenic yeast and fungi responsible for the infection in the oral cavity. A variety of antifungal agents are suitable for the present invention. Preferred are the polyene antifungals, especially nystatin and amphotericin B. Examples of other antifungal agents applicable to the methods of the invention include 5-fluorocytosine and imidazole- and triazole-derivative antifungal agents, especially naftifine, terbinafine, tolnafate, tolciclate, isoconazole, siliconazole, miconazole, clotrimazole, econazole, bifonazole, oxiconazole, tioconazole, ketoconazole, itraconazole, fluconazole, and terconazole, all known to the art. See, for example, Kostiala, I. et al., Acta Odontol. Scand. 37:87-101 (1979); and Bossche, H.V., CRC Crit. Rev. Microbiol. 15:57-72 (1987).

40 In another embodiment, combinations of more than one antifungal agent are used in the composition of the invention. Combinations of antifungal agents can be prepared, for example, for the purpose of providing treatment or protection against a broad spectrum of microfungal species, or for the purpose of attacking a 45 specific microfungal species with drugs acting through different modes of action. Combination of antifungal agents may also allow a lower dose of a given antifungal agent to synergistically act with a lower dose of another antifungal agent in a manner which is efficacious in combination but not separately.

45 The antimycotic composition may be formulated to include other drugs such as antibacterial or 50 antiseptic agents known to the art. See, for example, the section on "Quaternary Ammonium and Related Compounds" in the article on "Antiseptics and Disinfectants" in Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed. (Vol. 2, pp. 632-5).

55 Such materials have been used in oral compositions to counter bacteria in the oral cavity. Among the most common and efficacious of these antibacterial, quaternary ammonium compounds are cetylpyridinium chloride and benzalkonium chloride. Other cationic ammonium antibacterial agents of this type are mentioned, for instance, in U.S. Patent Nos. 2,984,639, 3,325,402, 3,431,208, 3,703,583, and 4,339,430, British Patent No. 1,319,396, and German Patent No. 2,332,383. Most preferred is cetylpyridinium chloride, which is efficacious, compatible with the other components of the oral composition, and inexpensive.

virtue of being a non-prescription drug. None of these compounds has been used before in sustained release, long-acting compositions. By long acting is meant a composition which provides efficacious levels of the active drug contained therein for a period of weeks, preferably at least 4 weeks, or 30 days.

It is also an aim of this invention that the aforementioned antifungal agent is released to the sites of 5 fungal lesions and pockets in a long-term sustained release manner so as to reduce the required frequency of use. Long-term sustained release is desirable because it improves patient compliance with the treatment protocol and it is more convenient for the patient. Hence the success of the treatment is more probable. The method of the invention may need only a single application of the oral varnish composition of the 10 invention to remain efficacious for a period of weeks. Other methods require a multi-dose application of paste every few days or ingestion of lozenges every four hours by the patient. At best, the pastes remain effective for 2-3 days and the lozenges only for hours.

In addition, by the composition and method of the invention, because of the long-term sustained release 15 of the drug, much lower amounts of the antifungal drug may be required for efficacious results. Conventional therapy uses doses of nystatin as high as 10^8 IU/dose. The concentrations of nystatin preferred in the invention are 2×10^5 I.U., with an acceptable range of 2×10^5 - 10^6 I.U. Because of the lower doses of nystatin, the side effects of the drug are eliminated or minimized. For example, at the efficacious concentrations of nystatin taught by the compositions and methods of the invention, in clinical evaluations there was no bitter-taste noted. The bitter taste of the drug is one of the major complaints of patients taking conventional 20 nystatin therapy.

20 Lastly, the physical form and manner of presentation of the composition of the invention may be advantageous for a patient with an oral microfungal infection. Often the area of the infection is so sore so as to make the direct application of a paste or even sucking lozenges, troches or pastilles very painful; rinsing with a mouthwash does not leave efficacious levels of the drug in the oral cavity. In other cases, oral treatments with mouthwashes, lozenges, pastes, troches or pastilles is very difficult or just not practical, for 25 example with infants or animals. The compositions of the invention may solve this problem by applying the antifungal drug to the teeth, gingival tissues or orthodontic appliance, for slow, long-term sustained release at efficacious levels into the salival fluids of the oral cavity. In addition the composition of the invention is colorless and visually undetectable by those unaware of the treatment.

Long term sustained release is accomplished by embedding the active drug agent(s) in a polymer. The 30 specific polymer used is not critical. Long term sustained release, may, in accordance with the present invention, be accomplished by embedding an anti-fungal agent in any biologically suitable polymer. For example, a hydrophobic polymer, a hydrophilic polymer, or a combination of hydrophilic and hydrophobic polymers, may be used to form sustained releases formulations that would be suitable as a varnish for oral 35 administration in accordance with the present invention. One or more proteinaceous polymers (such as gelatin, etc.), cellulosic polymers, acrylic polymers, etc. may be employed. Suitable polymers are disclosed in U.S. Patent Applications Serial Nos. 07/189,918; 07/304,091; 07/369,223; and 07/432,667.

Cellulosic or acrylic polymers are especially preferred for forming a varnish for oral administration. The 40 use of these polymers provides the advantage of allowing lower doses of a drug to be used and thus eliminating or minimizing side effects such as staining of teeth and dentures and unpleasant taste. A variety of suitable hydrophobic polymers are known in the art of oral compositions. Preferred are the insoluble and inexpensive polymers: hydrophobic type (poly-ethylene, polymethacrylate, polyamide-nylon, poly(ethylene-vinyl acetate) cellulose nitrate, silicones and others). Most preferred is ethyl cellulose. Another suitable polymer is methylacrylic acid polymer.

45 Thus in a preferred embodiment, an oral composition with the highly desirable characteristics comprises an antimycotic compound such as nystatin embedded in a sustained release cellulosic polymer such as ethyl cellulose, in a pharmaceutically effective vehicle. For example, nystatin, 100,000 IU (1-5 parts), and ethyl cellulose (5-9 parts) may be dissolved in ethanol (80-120 parts) for the preparation of sustained release varnish in film form.

For application to buccal and lingual surfaces of teeth, an ethanolic solution of the antimycotic agent 50 and cellulose polymer (containing up to 4% of the drug as used in the varnish) are applied with a soft brush or with a spray. Ethanol may be evaporated by a gentle stream of warm air. Mouthwash forms are not suitable because of the inefficient application of the composition to affected tissue areas. However, orthodontic appliances such as dentures may be dipped in a solution containing the composition of the invention.

55 The composition of the invention may be applied to teeth or dental appliances which act as a solid support and point of release for the antifungal agent in the composition throughout the treatment period. The tooth or orthodontic appliance varnished with the antifungal composition of the invention may be placed in direct contact with the site of infection, as for example, by placing dentures on top of an infected or

irritated gum for the treatment of denture stomatitis. Alternatively, the varnished tooth or dental appliance may act as a reservoir which releases efficacious levels of the antifungal agent in the salival fluids to other infected sites within the oral cavity or throat. Therefore, in a highly preferred embodiment, there is direct contact between the composition of the invention and the site of the microfungal infection. In another preferred embodiment, the composition of the invention is applied to a site removed from the infected area but within the range of the efficacious levels of antifungal drugs released by the composition. Orthodontic appliances within the scope of the invention include dentures, a set of dentures, bridges, braces, anchoring pins and the like. The appliance can be a temporary or permanent appliance. The compositions and methods of the present invention therefore provide a therapy for denture stomatitis, oral thrush, and other oral fungal diseases and conditions.

For application to orthodontic appliances, a total of about 40 mg of antimycotic agent such as nystatin or amphotericin B in an ethanol solution with ethyl cellulose may be applied per appliance by dipping, spraying or painting it on with a soft brush, and residual solvent removed with a gentle stream of warm air.

Those skilled in the treatment of diseases of the oral cavity will, without undue experimentation, be able to produce ranges of concentrations of other appropriate antifungal agents and sustained release polymers.

The thickness of the film as varnish can be varied according to the desired length of efficacious treatment or drug potency. In a preferred embodiment the film coating the tooth or appliance is 10-300 μm thick.

It is another feature of the invention that the oral compositions for treatment and prevention of fungal infections also provide for additional desirable components. For example, the adhesiveness of the oral composition may be improved by the incorporation within said composition of gums such as gum mastic in a formulation providing from 1-20% by weight of the gum mastic. Other suitable mastics are disclosed in U.S. Patent No. 4,315,779 to Heyd, D., et al., and U.S. Patent No. 4,374,844 to Wahni, H.V.R., et al.

The composition may include a demulcent/humectant (i.e., plasticizer) such as polyethylene glycol (e.g. 400-to-4000), glycerol, sorbitol, or mineral oil in concentrations of about 1% by weight. Other humectants, detergents, or surface-active agents will be known to those skilled in the formulation of oral compositions.

Thus, in a preferred composition, the oral composition of the invention comprises nystatin, ethyl cellulose polymer, an adhesive, a plasticizer, and solvent (i.e., aqueous ethanol). In a highly preferred formulation, gum mastic is also present. Water, flavorings, and coloring agents may also be present as required. Once applied to teeth or other orthodontic appliance, the varnish is not easily removed by normal dental hygiene protocols, such as brushing. The dry film can only be removed mechanically. In addition, because the varnish coats the surface of the teeth or orthodontic support with a smooth surface and the same contours of the support, it adds no uncomfortable, unfamiliar or otherwise annoying geometry to the oral cavity, in the manner that a paste can.

The composition and methods of the invention may also be applied as a preventative or deterrent measure, especially in patients highly susceptible to opportunistic infections of the oral cavity by microfungi.

The varnish of the invention may also be applied extraorally to sites of microfungal infection, for example, to infected nails on the fingers and toes of patients with chronic mucocutaneous candidosis. Alternatively, the composition of the invention, especially in combination with antibacterial agents, may be provided on a varnished pad or bandage or patch which is placed in contact with the site of infection, for example, topically or intravaginally.

A preferred composition suitably comprises:

- (a) an antimycotic agent, eg. nystatin, in an amount of from 2 to 3% w/v;
- (b) a hydrophobic polymer, such as ethyl cellulose, in an amount of from 5 to 6% w/v;
- (c) advantageously a plasticiser such as polyethylene glycol, in an amount of from 0.5 to 1.0% w/v;
- (d) a solvent, preferably an alcohol such as ethanol.

(Amounts in %w/v are based on the solvent.)

The invention will now be described, by way of example only, with reference to the accompanying Examples which are to be interpreted as merely illustrative, and not limiting, on the present invention.

Example 1

55

Varnish Preparation

The following formulations (Table 1) were all prepared by the same general procedure as follows: ethyl cellulose and polyethylene glycol polymers were dissolved in the suitable solvent. After complete dissolution of the polymers, the additional components of the varnish are added.

Ethyl cellulose - EC
Polyethylene glycol - PEG
Nystatin - NYS

TABLE 1

15	MATERIAL/FORMULATION		I	II	III	IV	V	VI	VII	VIII	IX	X
	NYS (G)	1.5	2.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	4.0
	EC-NF100 (G)	8.5	7.0	6.0	6.0	6.0	5.0	6.0	6.0	6.0	6.0	6.0
	PEG 400 (G)	0.5	1.0	1.0	1.0	1.0	1.0	1.0	---	---	---	---
	PEG 4000 (G)	---	---	---	---	---	---	1.0	1.0	1.0	1.0	---
	GUM MASTIC	---	---	---	---	---	1.0	---	---	1.0	1.0	---
20	ETHANOL (C°C)	100	100	100	80	120	100	100	100	100	100	100

Example 2

Evaluation of the Varnish in Vitro Sustained Release Activity of Nystatin on *Candida Albicans* in Vitro

Films containing Nystatin were cast from the varnish formulation IV on glass plates using the technique of Konig et al., *J. Pharm. Sci.* 51:77 (1962). The solvent was allowed to evaporate at room temperature and the residual film removed from the plate. A strain of *C. albicans* isolated from clinical material was used in this study. A 1:10 dilution of an overnight growth stock suspension of the above organism was mixed with mycological culture medium (Sabouraud) and poured into petri dishes. Five mm diameter disks of the films containing Nystatin were placed on the hardened medium.

After 24 h or 48 h, films were transferred onto another set of petri dishes containing the same medium plus *C. albicans* suspension as in the first set.

plus *C. albicans* suspension as in the first set. Inhibition zones were recorded after incubation periods of 24 and 48 h at 37°C. All films were used in duplicate. The mean inhibition zone is summarized in Table 2.

TABLE 2

Example 3

5

Clinical Study: Evaluation of the Varnish in vivo

Preparation of coated denture. The Nystatin varnish (Formulation IV) was applied to the denture base facing the mucosa, by means of a soft brush. Removal of the solvent was achieved by a gentle stream of hot air.

10 The dentures were weighted before and after coating and the total amount of coating calculated. Forty mg of Nystatin per denture was the average amount of drug used. (Equivalent to 200,000 I.U.)

In the preliminary clinical evaluation of the system, 5 patients suffering from denture stomatitis were selected from an old age home. Three tests were performed on each patient: a) 1 swab from upper gum, b) 15 1 swab from denture, and c) 2 ml of saliva was collected.

Material from the swabs was washed into a solution containing 0.2% neopeptone + 0.8% Tween 80, which was also used for further dilution of this material and of the saliva. Ten ml aliquots of the various dilutions were inoculated in duplicate onto plates containing bacteriological blood agar (for bacterial isolation) and plates containing mycological medium Sabouraud (for C. albicans isolation).

20 All plates were incubated for 48 h at 37 °C and the number of bacterial and yeast colonies recorded.

The effects of the local application of a sustained-release delivery system of nystatin on fungal growth due to denture stomatitis in these patients are summarized in Table 3.

In summary there was an improvement in clinical status of the disease was observed, total elimination of Candida in saliva, gum and denture with no change in the normal bacteria flora levels. There was an 25 improved compliance on the part of the patient: one single application is a much more convenient way of treatment compared to the conventional multi-dose application, and this new way of treatment is not dependent on the patient's cooperation.

Much lower amounts of Nystatin are necessary for the clinical effect as compared to the total of 10⁸ I.U. used in conventional therapy. Lastly, no side effects, such as the bitter taste of Nystatin were observed in 30 the preliminary clinical evaluation of this system.

These results are consistent with inhibition of fungal growth in the oral cavity of these patients by this form of the drug and further suggest that efficacious concentrations of the drug on the tooth/tissue surface is achieved creating a local antimycotic effect.

35

40

45

50

55

TABLE 3
EFFECT OF VARIOUS DENTURE WEARERS AFTER SINGLE APPLICATION OF SUSTAINED RELEASE VARNISH OF NYSTATIN

Patient	Bacteria*	0		2days		3days		7days	
		Candida*(1)	Bacteria	Candida	Bacteria	Candida	Bacteria	Candida	Bacteria
1	G	7.1 x 10 ⁸	1.0	7.1 x 10 ⁷	0	1.2 x 10 ⁶	0	8.2 x 10 ⁶	0
	D	5.5 x 10 ⁷	2.9	1.2 x 10 ⁸	0	8.0 x 10 ⁷	0	6.3 x 10 ⁷	0
	S	5.5 x 10 ⁷	2.4	4.1 x 10 ⁷	0.25	7.5 x 10 ⁷	0.9	2.2 x 10 ⁸	1.6
2	G	2.2 x 10 ⁶	28.8	2.0 x 10 ⁶	0	1.1 x 10 ⁷	0	5.1 x 10 ⁶	0
	D	4.1 x 10 ⁶	19.9	4.1 x 10 ⁶	0	1.2 x 10 ⁶	0	3.2 x 10 ⁶	0
	S	1.4 x 10 ⁸	21.1	1.2 x 10 ⁷	5.2	1.1 x 10 ⁷	3.0	2.3 x 10 ⁷	6.1
3	G	3.3 x 10 ⁷	16.2	3.2 x 10 ⁷	0	3.1 x 10 ⁷	0	8.0 x 10 ⁷	0
	D	2.6 x 10 ⁷	11.8	2.4 x 10 ⁷	0	1.2 x 10 ⁷	0	2.3 x 10 ⁷	0
	S	3.1 x 10 ⁷	10.1	1.0 x 10 ⁷	6.1	2.2 x 10 ⁷	2.4	8.6 x 10 ⁶	2.0
4	G	4.2 x 10 ⁷	6.5	4.4 x 10 ⁷	0	8.1 x 10 ⁷	0	6.2 x 10 ⁷	0
	D	6.2 x 10 ⁷	9.2	7.1 x 10 ⁷	0	1.2 x 10 ⁸	0	7.2 x 10 ⁶	0
	S	2.1 x 10 ⁸	4.2	5.2 x 10 ⁷	2.6	6.1 x 10 ⁷	1.8	9.0 x 10 ⁷	2.0
5	G	4.2 x 10 ⁷	12.6	8.0 x 10 ⁶	0	2.2 x 10 ⁷	0	2.1 x 10 ⁷	0
	D	7.2 x 10 ⁷	17.2	6.2 x 10 ⁶	0	6.1 x 10 ⁶	0	1.6 x 10 ⁷	0
	S	5.2 x 10 ⁶	10.8	3.2 x 10 ⁶	2.8	6.4 x 10 ⁶	5.2	2.0 x 10 ⁷	4.3

* Candida and Bacteria determined from the same sample

(1) Calculated from $\frac{\text{Cardida counts}}{\text{Bacteria counts}} \times 10^4$

Gum
Denture
Sputum

Claims

5 1. A sustained release antifungal varnish composition comprising:
 (a) an antimycotic drug;
 (b) a sustained release hydrophobic polymer;
 and a pharmaceutically acceptable carrier.

10 2. A sustained release antifungal varnish composition comprising:
 (a) an antimycotic drug;
 (b) a sustained release hydrophobic polymer;
 and a pharmaceutically acceptable carrier for use in human or veterinary medicine.

15 3. A composition as claimed in claim 1 or 2 wherein the antimycotic drug is nystatin, amphotericin B, miconazole or clotrimazole.

20 4. A composition as claimed in any of claims 1 to 3 wherein the hydrophobic polymer is polyethylene, polymethacrylate, ethyl cellulose, polyamide-nylon, poly(ethylene-vinyl acetate) cellulose nitrate, or a silicone.

25 5. A composition as claimed in any of claims 1 to 4 wherein the pharmaceutically acceptable carrier is water, ethyl alcohol, or an ethyl alcohol and water.

30 6. A composition as claimed in any of claims 1 to 5 additionally comprising a flavouring agent, a surface active agent, a colouring agent, a plasticizer such as polyethyleneglycol, glycerol, sorbitol or mineral oil, or an adhesive gum such as gum mastic.

35 7. The use of a composition comprising:
 (a) an antimycotic drug;
 (b) a sustained release hydrophobic polymer; and
 a pharmaceutically acceptable carrier in the preparation of a sustained release antifungal agent for the treatment of a microfungal infection.

40 8. The use of claim 7 wherein the microfungal infection is denture stomatitis.

45 9. The use of claim 7 or 8 wherein the microfungal infection is from Candida, such as Candida albicans, or Torulopsis glabrata.

50 10. An orthodontal appliance having a surface at least partially coated with a sustained release antifungal composition comprising:
 (a) an antimycotic drug;
 (b) a sustained release hydrophobic polymer,
 (c) a pharmaceutically acceptable carrier.

Claims for the following Contracting States : GR, ES

40 1. A process for the preparation of a sustained release antifungal varnish composition, the process comprising admixing:
 (a) an antimycotic drug;
 (b) a sustained release hydrophobic polymer;
 and a pharmaceutically acceptable carrier.

45 2. A process as claimed in claim 1 or 2 wherein the antimycotic drug is nystatin, amphotericin B, miconazole or clotrimazole.

50 3. A process as claimed in claim 1 or 2 wherein the hydrophobic polymer is polyethylene, polymethacrylate, ethyl cellulose, polyamide-nylon, poly(ethylene-vinyl acetate) cellulose nitrate, or a silicone.

55 4. A process as claimed in any of claims 1 to 3 wherein the pharmaceutically acceptable carrier is water, ethyl alcohol, or a mixture thereof.

60 5. A process as claimed in any of claims 1 to 4 additionally comprising a flavouring agent, a surface active agent, a colouring agent, a plasticizer such as polyethylene glycol, glycerol, sorbitol or mineral oil, or an adhesive gum such as gum mastic.

65 6. The use of a composition comprising:
 (a) an antimycotic drug;
 (b) a sustained release hydrophobic polymer; and a pharmaceutically acceptable carrier in the preparation of a sustained release antifungal agent for the treatment of a microfungal infection.

70 7. The use of claim 6 wherein the microfungal infection is denture stomatitis.

8. The use of claim 6 or 7 wherein the microfungal infection is from Candida, such as Candida albicans, or Torulopsis glabrata.

9. An orthodontal appliance having a surface at least partially coated with a sustained release antifungal varnish composition comprising:

- 5 (a) an antimycotic drug;
- (b) a sustained release hydrophobic polymer; and
- a pharmaceutically acceptable carrier.

10. A method of making an orthodontal appliance, the method comprising applying to at least a part of a surface of an orthodontal appliance a sustained release antifungal varnish composition comprising:

- 10 (a) an antimycotic drug;
- (b) a sustained release hydrophobic polymer; and a pharmaceutically acceptable carrier.

15

20

25

30

35

40

45

50

55



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL.5)
X	STN INTERNATIONAL INFORMATION SERVICES DATA BASE: CHEMICAL ABSTRACTS, Accession number: 104:95515z; & JP-A-60 228 412 (TERUMO CORP.) 13-11-1985 * Abstract * ---	1-7	A 61 K 6/00 A 61 K 9/70 A 61 K 31/415 A 61 K 31/71 A 61 K 47/32 A 61 K 47/34 A 61 K 47/38
Y	EP-A-0 298 271 (HOECHST) * Claims 1,3-4; page 5, lines 36-38,42-45; page 6, lines 1-6 * ---	1-7	
Y	STN INTERNATIONAL INFORMATION SERVICES DATA BASE: CHEMICAL ABSTRACTS, Accession number: 110: 63729e; & JP-A-63 044 518 (SEKISUI CHEMICAL CO., LTD) 25-02-1988 * Abstract * -----	1-7	
			TECHNICAL FIELDS SEARCHED (Int. CL.5)
			A 61 K
<p>The present search report has been drawn up for all claims</p>			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	09-05-1990	SCARPONI U.	
CATEGORY OF CITED DOCUMENTS			
<p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p>			
<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p>			
<p>& : member of the same patent family, corresponding document</p>			